10/579510

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2004/037200	International filing date *(day/month/year)* 01.12.2004
Priority date *(day/month/year)* 10.12.2003	
International Patent Classification (IPC) or both national classification and IPC C12N15/12, C07K14/50, A61K38/18, C12N1/19	
Applicant ELI LILLY AND COMPANY	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/037200

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. (13-14, 26-27 and 36-37) partially

because:

☒ the said international application, or the said claims Nos. 13-14, 26-27 and 36-37 (in relation to ind. applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-41
	No: Claims	
Inventive step (IS)	Yes: Claims	1-41
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-12,15-25, 28-35, 38-41
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III
Non-establishment of opinion with regard to industrial applicability

Claims 13, 14, 26, 27, 36 and 37 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the present claims 13, 14, 26, 27, 36 and 37 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are considered relevant:

D1: WO 03/011213 A (ELI LILLY AND COMPANY; GLASEBROOK, ANDREW, LAWRENCE; HAMMOND, LISA, JA) 13 February 2003 (2003-02-13)
D2: WO 01/36640 A (CHIRON CORPORATION KYOTO UNIVERSITY) 25 May 2001 (2001-05-25)
D3: WO 03/059270 A (ELI LILLY AND COMPANY; HEUER, JOSEF, GEORG; KHARITONENKOV, ALEXEI) 24 July 2003 (2003-07-24)

Novelty and inventive step

The subject-matter of present application is novel. Claims 1-41 meet the requirements of article (33(2) PCT).

Document D1 is regarded as the closest prior art. D1 defines on page 6 lines 28-32 and on page 9 lines 8-26 the possiblity of introducing conservative mutations in the sequence of FGF-21. The difference between D1 and the present application is the provision of FGF-21 muteins at specific positions. The problem to be solved by the present invention may therefore be regarded as the provision of further FGF-21 muteins having a higher stability in pharmaceutical formulation conditions (i.e. in the presence of m-Cresol).
Example 6 shows (table 4) some FGF-21 muteins having reduced aggregation (reduced average particulate diameter) and nothing about all the other muteins being claimed. Notwithstanding, an inventive step can be acknowledged for those specific substitutions (example 6) showing a reduced aggregation indicating a higher stability.

Clarity and support by the description

Claims 1,15 and 28 are not clear. They do not meet the requirements of Article 6 PCT. Their wording "...substitution of a charged and/or polar but uncharged amino acid...." is very confusing and could allow e.g GLY 42 to be replaced by CYS (i.e. the substitution of a uncharged polar amino acid with a uncharged polar amino acid) which is a conservative substitution as it is explained in D1 (page 9 lines 7-21). Furthermore most of these claimed muteins have not been disclosed in the description and lack also support (article 6 PCT). The same drafting as in claim 4 or 16 would be a good solution to overcome the above problems of clarity.

Re Item VIII
Certain observations on the international application

The expression " a biologically active peptide thereof " (claims 1, 15 and 28) is not acceptable (article 6 PCT) because it is vague and unclear.